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Seizure 2001; **10**: 420–423
doi:10.1053/seiz.2000.0527, available online at http://www.idealibrary.com on IDEAL®

Concentric visual field restriction under vigabatrin therapy: extent depends on the duration of drug intake

STEFAN TOGGWEILER & HEINZ-GREGOR WIESER

Neurology Clinic, Department of Epileptology and Electroencephalography, University Hospital Zürich, Switzerland

Correspondence to: Professor Dr med. H. G. Wieser, Abteilung für Epileptologie & Elektroenzephalographie, Neurologische Klinik, Universitätsspital, CH-8091, Zürich. *E-mail*: hgwepi@neurol.unizh.ch

Vigabatrin (VGB) is a novel antiepileptic drug which inhibits GABA-transaminase (GABA-T) and thus increases the level of GABA in the CNS and in its neurons. In the last few years, evidence has been presented that VGB intake may be associated with concentric visual field restrictions. The aim of this study was to estimate the prevalence of visual field constrictions and to determine if, and to what extent, they depend on the duration of VGB treatment. Visual fields of 15 patients who were taking VGB, and 12 matched control patients who had never been exposed to VGB, were investigated using a kinetic Goldmann perimeter. One of the 12 matched control patients had a slightly restricted visual field whereas nine of the 15 VGB patients (60%) showed a moderate to severe concentric visual field restriction. The extent of the outer isopters (V4, I4, I3, I2) depended on the duration of VGB intake. VGB treatment was clearly associated with a high prevalence of concentric visual field restriction. Moreover, the degree of visual field restriction depended on the duration of VGB intake. Further work, including longitudinal studies, is needed to clarify whether these lesions are reversible or not.

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Key words: epilepsy; vigabatrin; visual field restriction; seizures; GABA.

INTRODUCTION

Vigabatrin (VGB) is an irreversible inhibitor of GABA-transaminase (GABA-T) and thereby increases the level of the major inhibitory neurotransmitter GABA. After Eke *et al.*[1] reported three patients with concentric visual field losses following VGB therapy, several studies showed visual field constriction during VGB therapy. In 1999, Hoechst Marion Roussel reported the overall prevalence to be up to 28% with a 95% confidence interval between 20% and 36%[2]. In 1999, Lawden, Eke, Degg and colleagues[3] presented a study which investigated 33 VGB patients and 16 controls with static perimetry, electrooculograms, electroretinograms and visual evoked responses. Twelve (39%) of the 31 VGB patients had a definite bilateral field defect with temporal and macular sparing and none of the 16 control patients showed any visual field losses. In a study by Kälviäinen *et al.*[4], 13 of 32 VGB patients (41%) had concentric visual field defects but there was only weak correlation between the duration of VGB therapy and the extent of visual field defects in both eyes. Another study by Miller *et al.*[5] with 39 VGB patients revealed that nearly 50% had constricted visual fields.

PATIENTS AND METHODS

Seventeen patients who were taking or who had previous exposure to VGB therapy and 12 control patients, all attending the Department of Neurology at the University Hospital of Zurich, were identified and investigated by a manual kinetic Goldmann perimeter (Haag-Streit, Bern, Switzerland). Two patients from the VGB group had to be excluded because they both had homonymous hemianopsia. Fifteen VGB patients and 12 control patients remained. At the time of the investigation, the investigator was aware of which group the patients belonged to. All 27 patients were suffering from a partial epilepsy with simple partial or complex partial seizures, a few with occasional secondary generalization. The patients on VGB therapy were chosen at random. The patients for the control group were

1059–1311/01/060420 + 04 $35.00/0
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chosen to match in age, concomitant medication, history of seizures and history of relevant operations. As the epilepsy unit of the University Hospital Zurich is a referral centre for epilepsy surgery in patients suffering from a partial epilepsy, most of the patients have a history of a selective amygdalo-hippocampectomy (AHE)[6]. This operation can cause homonymous contralateral upper quadrant defects.

For analysis of the Goldmann perimetry, we measured the temporal, superior, nasal and inferior range of each isopter (V4, I4, I3, I2, I1) of both eyes separately. In addition, the mean extent of each isopter was obtained by measuring the radial extent at 12 points of the visual field, 30 degrees apart. The mean visual field extents were calculated by averaging each of these 12 points.

Statistical analysis was done with SPSS for Windows 9.0 (Mann–Whitney test corrected for ties, Fisher's exact test, one-way analysis of variance (ANOVA), repeated measures ANOVA with Greenhouse-Geisser's correction, Pearson correlation). The significance level was fixed to be $\alpha = 0.05$. In certain analyses, Bonferroni's correction was used, which is defined as follows: let k denote the number of performed tests, then the corrected significance level α^* is computed as $\alpha^* = \alpha/k$.

RESULTS

The age of the patients ranged from 13 to 52 years in the VGB group and from 12 to 52 years in the control group. (Mann–Whitney test, $P = 0.45$). There were seven men and five women in the control group and nine men and six women in the VGB group (Fisher's exact test, $P = 1.00$). From the 15 VGB patients, one had simple partial seizures, 11 had complex partial seizures and three suffered from occasional secondary generalization. Among the 12 control patients, there were three with simple partial, six with complex partial seizures and three suffering from secondary generalization.

Only five of the 15 VGB patients were taking VGB on a daily basis at the time of the evaluation. Of those, four were taking 2 g and one was taking 2.5 g per day. The remaining ten patients had stopped taking the drug 7–48 months previously. In these cases, the drug was withdrawn mostly because of a general reduction in antiepileptic drug (AED) regimen, and in a few cases because of ineffectiveness. In none of the patients was VGB discontinued because of any visual symptoms. Mean length of treatment with VGB was 47.2 months, ranging from 13 to 94 months and the daily dose taken during this time was either 2 g or 2.5 g. Thus, the total amount of VGB taken ranged from 780 g to 5640 g (mean 3062 g).

Table 1: Extent of visual fields in VGB and control patients (V4 object).

Meridian	Control ($n = 12$)	VGB ($n = 15$)
Temporal	86.8 ± 4.5	69.2 ± 13.0[a]
Superior	45.3 ± 5.2	41.9 ± 7.6[a]
Nasal	56.3 ± 4.3	46.8 ± 9.5[a]
Inferior	68.3 ± 5.3	57.0 ± 12.7[a]
Mean	63.3 ± 2.7	53.8 ± 9.6[a]

Data presented is the mean extent $\pm$ SD.
[a] Significant at the 0.05 level compared with control (Mann–Whitney test).

Eleven patients were taking other AEDs in addition to VGB. Of these 11 patients, eight were also taking carbazepine. Other drugs frequently taken by these patients were valproate and phenytoin. The AED regimen also included clobazam, lamotrigine, phenobarbital, topiramate, ethosuximide. Among the control patients carbazepine, valproate and phenytoin were the most commonly used AED.

Ten of the 15 VGB patients had undergone a selective AHE before the perimetry was performed. One had had a parietal operation on the right side. Of the nine control patients, eight had undergone a selective AHE. Among the patients in the VGB group, 14 had no subjective visual problems. One was bumping into objects quite frequently. None of the control patients complained about visual problems. The minimal visual field restriction in the superior part of the visual field, which can result from a selective AHE, was not noticed by any of the patients.

In order to estimate how much the mean visual field extent of the VGB patients differs from the mean visual field extent of the control patients, a repeated measures ANOVA with the Greenhouse-Geisser correction was carried out. There was a significant difference between the VGB group and the control group. The VGB patients had narrower isopters than the control patients ($P = 0.015$). *Post hoc* analysis with Bonferroni's correction was performed. The mean extent of each isopter was compared to the control group. Only mean visual field extents of the V4 object differed significantly ($\alpha^* = 0.01$; Mann–Whitney test, $P = 0.009$) whereas mean visual field extents for the other isopters did not differ significantly ($\alpha^* = 0.01$; I4, $P = 0.013$; I3, $P = 0.083$; I2, $P = 0.222$; I1, $P = 0.922$). Thus, the outermost part of the visual field was the most affected part.

The mean extent of the visual field and each of the four meridians, obtained when using the V4 object of the perimeter, were analysed separately (Table 1). There were significant differences between the two groups for the mean extent ($P = 0.007$) and for the four meridians (temporal, $P = 0.000$; superior, $P = 0.236$; nasal, $P = 0.014$; inferior, $P = 0.012$). Figure 1 shows the mean visual field extent in both collectives.

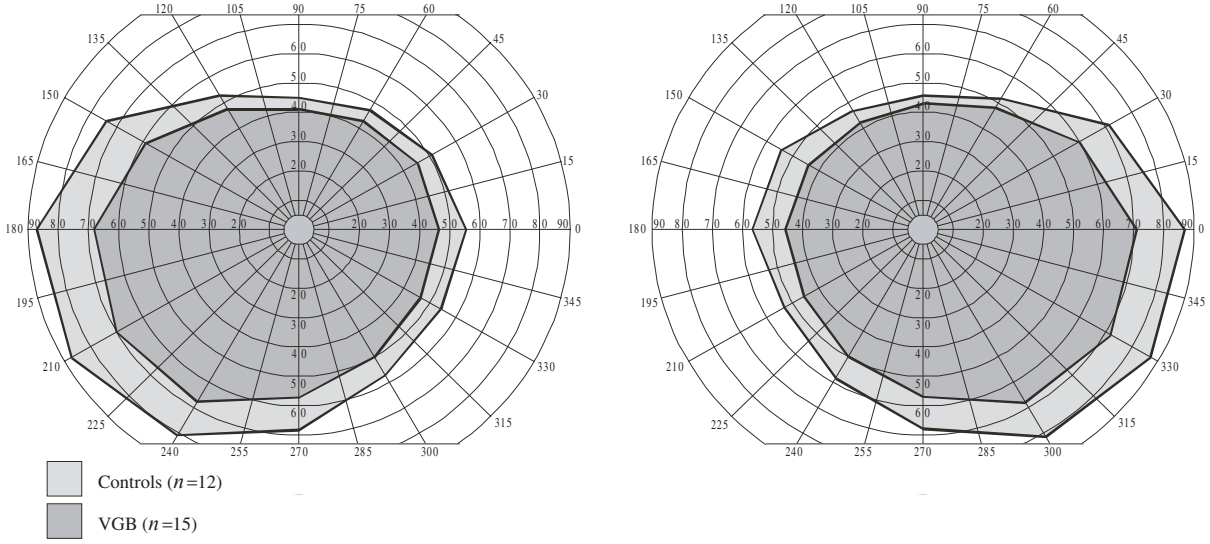

Fig. 1: Mean visual field extent* (V4 object).

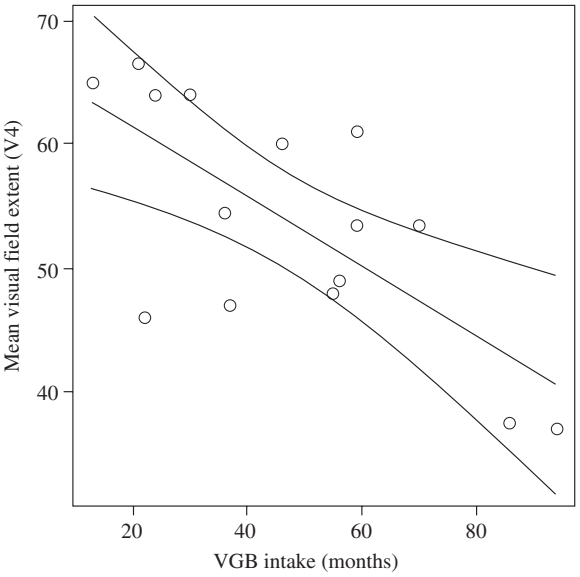

Fig. 2: Dependence of the mean visual field extent on the duration of VGB intake. The mean visual field extent (V4 object) depends on the duration of the VGB intake. Linear regression with a 95% prediction interval is presented. Mean visual extent $= 67.08 - 0.28 \times$ VGB intake (months). R-square $= 0.50$.

To estimate if the visual field restriction depends on the duration of VGB intake, only data from the VGB collective were taken into consideration. A repeated measures ANOVA with covariate (duration of VGB intake) was carried out. There was a significant decrease of the visual field extents of all isopters according to the duration of VGB intake ($B = -0.24$, $P = 0.006$). Each isopter was tested individually. There was a high significance for V4, I4, I3 and I2 isopters ($\alpha^* = 0.01$; V4, $B = -0.28$, $P = 0.003$; I4, $B = -0.30$, $P = 0.006$; I3, $B = -0.30$, $P = 0.003$; I2, $B = -0.259$, $P = 0.010$). However, the innermost isopter did not show a significant dependence on the duration of drug intake ($\alpha^* = 0.01$; I1, $B = -0.071$, $P = 0.309$). The dependence of the mean visual field extent on the duration of VGB intake is shown in Fig. 2.

DISCUSSION

The results of the prospective cross-sectional study suggest that VGB treatment is associated with concentric visual field restriction. Furthermore, this study shows that the degree of visual field loss depends on the duration of VGB intake.

Most of the patients in the VGB group had narrowed isopters in comparison to the control patients. This effect was most obvious in the outermost (V4) isopter and less obvious in the inner isopters (I4, I3, I2). There was no difference between the two collectives in the innermost isopter (I1). Thus VGB leads not only to a concentric visual field restriction but also to a diffuse decreased sensitivity in the inner parts of the visual field. As the results from the V4 isopter shows, the temporal and the inferior meridian were the most affected parts.

In this study, nine (60%) of the 15 examined VGB patients had concentric visual field restriction with a mean visual field extent ranging from 37 to 54.5 degrees. The other six VGB patients had a mean visual field extent of 60 degrees or more. Eleven of the 12 control patients had a mean visual field extent of 60 degrees or more, and one had a mean visual field extent of 56.5 degrees. The visual field constriction which was detected by kinetic perimetry was asymp-

tomatic in all patients except for one. Only one patient in the VGB group complained about bumping into objects frequently.

There was a strong dependence of the degree of the visual field restriction and the duration of VGB medication. All but the innermost isopter were more narrowed when the duration of VGB intake increased. In this study, the visual field showed an average restriction of each isopter of about 3–4 degrees per year of VGB intake.

This study has limitations. First, the number of patients examined was relatively small. However, the statistical analysis was carried out carefully and Bonferroni's correction was used where necessary. Second, most of the patients in the VGB and in the control group had undergone a selective amygdalohippocampectomy, which can reduce visual field in the sense of an upper homonymous quadrantanopsia.

Thus far, two cases with an improvement of visual field constriction after the discontinuation of VGB have been described by Krakow and colleagues[7]. This suggests that vigabatrin-associated retinal changes may be at least partly reversible in some patients after the drug has been discontinued. In another study, the visual fields of 13 patients who stopped taking VGB were not improved after several months of withdrawal[8]. Research is needed to clarify the mechanism of the concentric visual field restrictions which occur under VGB treatment. Longitudinal section studies could help to determine if and to what extent there is reversibility. Baseline visual field testing before VGB is administered allows the determination of the exact extent of visual field losses.

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